## REMARKS

Claim 5 has been canceled herein. Such cancellation is without prejudice on the merits to further prosecution of this claim in one or more continuing applications.

Claims 4, 6, and 11 have been amended herein. Specifically, Claims 4 and 6 have been amended to indicate that the substituents $R^{15}$ and $R^{16}$ cannot simultaneously be hydrogen. This amendment is introduced to draw a clear distinction between the present claims, and the Huck et al. paper. In support of this negative limitation, please see MPEP §2173.05(i) and the cases cited therein:

> If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. See *In re Johnson*, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining."). See also *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983), *aff'd mem.*, 738 F.2d 453 (Fed. Cir. 1984).

The definition of the "Y" substituent has also be amended in Claims 4 and 6 to be solely a single bond.

Because independent Claim 6 has been amended, the scope of dependent Claims 8 and 9 has been correspondingly altered. Applicant therefore request that Claims 8 and 9 be rejoined and examined on the merits. Applicants likewise request that Claim 11 (which has been amended to depend from Claim 4) be rejoined.

Claims 4, 6, 8, and 9 remain active in the application. Favorable reconsideration is respectfully requested.

The following comments address the issue presented in the Office Action in the order of their appearance:

**Information Disclosure Statement:**

The Office did not formally consider the Exhibits that Applicants submitted with their prior response. (See the bottom of page 2 of the Office Action dated May 5, 2006.) Submitted herewith is a Supplemental Information Disclosure Statement presenting for the Office's formal consideration the documents submitted as Exhibits B, C, and D of Applicants' prior response. (Exhibit A of Applicants' prior response was simply a courtesy copy of the Court's decision in *In re Wilder*, 222 USPQ 369 (CAFC 1984), which the Office cited earlier.) A copy of the Seebach et al. paper, referenced in Dr. Gellman's

Rule 132 Declaration, is also included in the IDS. Formal entry and consideration of these documents is respectfully requested.

To make the record complete, Applicants note that the Office's refusal to consider the Exhibits earlier runs contrary to MPEP §609.05(c), which states (emphasis added):

> Occasionally, documents are submitted and relied on by an applicant when replying to an Office action. These documents may be relied on by an applicant, for example, to show that an element recited in the claim is operative or that a term used in the claim has a recognized meaning in the art. Documents may be in any form but are typically in the form of an affidavit, declaration, patent, or printed publication.
>
> **To the extent that a document is submitted as evidence directed to an issue of patentability raised in an Office action, and the evidence is timely presented, applicant need not satisfy the requirements of 37 CFR 1.97 and 37 CFR 1.98 in order to have the examiner consider the information contained in the document relied on by applicant.** In other words, compliance with the information disclosure rules is not a threshold requirement to have information considered when submitted by applicant to support an argument being made in a reply to an Office action. However, consideration by the examiner of the document submitted as evidence directed to an issue of patentability raised in the Office action is limited to the portion of the document relied upon as rebuttal evidence; the entirety of the document may not necessarily be considered by the examiner.
>
> At the same time, the document supplied and relied on by applicant as evidence need not be processed as an item of information that was cited in an information disclosure statement. The record should reflect whether the evidence was considered, but listing on a form (e.g., PTO-892, PTO-1449, or PTO/SB/08A and 08B) and appropriate marking of the form by the examiner **is not** required.

Applicants respectfully note that the Exhibits attached to their prior response were submitted both for the Examiner's convenience and to bolster (using objective evidence) Applicants' reply to the issues raised in the prior Office Action. Because a Request for Continued Examination was filed in this matter, along with a request to consider Applicants' prior response, the Exhibits were presented in a timely fashion. Therefore, the Exhibits should have been considered on their merits earlier pursuant to MPEP §609.05(c).

**Election of Species Requirement and Expanded Search:**

In light of the amendment to Claim 6, Applicants request that Claims 8 and 9 be rejoined and considered on the merits. MPEP §803.02 states that

> Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim.

As discussed below, Applicants have amended the Markush groups to overcome the rejection under §102(b) in view of the Huck et al. paper. (The paper discloses only one relevant molecule, the Ac-Val-Nip-Nip-Leu-$N(Me)_2$ tetramer noted by the Examiner.) Re-examination of the Markush group, including Claims 8 and 9, is respectfully requested.

**Rejection of Claims 4-6, 8, and 9 Under 35 USC §101 (Utility) & §112, First Paragraph (Enablement):**

Applicants respectfully traverse these two rejections. Because the rejection under §112, first paragraph is predicated entirely upon the rejection under §101, these two rejections will be addressed simultaneously.

In response to the Office's comments at page 4 of the Final Office Action, Applicants again respectfully submit that the Office's dismissal of the Seebach et al. reference is improper. (The reference, submitted earlier as contemporary evidence of an established utility is Seebach et al. (2003) *Angew. Chem. Int. Ed.* 42(7):776-778.) Specifically, the Office states that the Seebach reference is inapplicable because:

> The compounds of Seebach are γ-dipeptides, while the instantly claimed compounds are, at a minimum, tetrapeptides with at least 1 α-amino acid and at least two cyclically-constrained β-amino acids. The compounds are not co-extensive or commensurate in scope, and thus cannot provide a "well-established utility" for the instant compounds based upon structure and amino acid content.

Applicants respectfully traverse this conclusion because it applies an improper standard for showing a well-established utility. If Applicants were able to produce a contemporaneous document that disclosed compounds that were "co-extensive" in scope with the claimed compounds in order to establish a well-established utility, the Office would promptly issue a §102 rejection in view of such a document. In effect, the Office is requiring Applicants

to produce an anticipatory reference in order to show that a well-established utility exists for the presently claimed compounds.

The standard articulated by the MPEP is not so stringent. MPEP §2107(II) dictates that an invention has a well-established utility if: (i) a person of ordinary skill in the art would immediately appreciate *why* the invention is useful based on the characteristics of the invention (*e.g.*, properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.

Addressing these two prongs in order, Applicants note that the Seebach et al. reference refers to compounds that are *similar* to those currently claimed. Seebach's compounds are in the same class as the presently claimed compounds, namely polypeptides that contain 1 or 2 extra methylene carbon atoms in the backbone of certain residues, that is, polypeptides containing β-amino acids and/or γ-amino residues. The Office is correct that the Seebach et al. paper describes dipeptides comprising γ-amino acid residues. The Office, however, is not entirely correct that the present claims are limited (at a minimum) to tetrapeptides containing at least one α-amino acid and two β-amino acids. See page 4 of the Office Action. Present Claim 6 explicitly includes within its scope tetramers including two cyclically-constrained γ-amino acid residues. Thus, Applicants respectfully submit that the compounds described by Seebach et al. (γ-amino acid dipeptides) are at least within the same general category or class of compounds as the presently recited compounds (tetramers that include two cyclically-constrained γ-amino acid residues).

There are also other contemporaneous documents that show the same well-established utility as articulated in the present application for compounds that are within the same structural class as those now claimed. See, for example, U.S. Patent No. 6,958,384. A courtesy copy of this patent is attached hereto as Exhibit A (and is also listed in the supplemental IDS submitted herewith.) Applicants submit that the '384 Patent is far more relevant on the question of utility than is the Schmitt et al. paper cited by the Office because the Schmitt et al. paper is admittedly not contemporaneous with the filing of the present application. (See the bottom of page 4 of the Office Action.)

The application that matured into the '384 Patent was published on November 13, 2003 (less than three months after the filing date of the present application). The '384 Patent is therefore contemporaneous in time with the present application. Because it is an issued patent, the '384 Patent and the claims it contains are presumed to be valid and to comply with all of the requirements of §101 and §112. See 35 USC §282: "A patent shall be presumed valid."

The claims of the '384 Patent are directed to unnatural polypeptides comprised entirely of γ-amino acid residues. In short, the compounds described and claimed in the '384 Patent are comprised entirely of non-constrained and cyclically-constrained γ-amino acid residues. See Claim 1 of the '384 Patent, which starts at col. 44, line 56. Of particular relevance to the present issue of utility, note that the utility articulated in the '384 Patent is **identical** to the utility recited in the current application. For example, see the '384 patent at col. 12, lines 5-40:

> The utility of these compounds [the γ-polypeptide homo-oligomers] for probing protein interactions is great because, as noted above, the γ-peptides adopt structures analogous to those seen in natural proteins and peptides. Thus, the subject compounds mimic natural protein conformations in solution, but are resistant or immune to proteolytic degradation by proteases and peptidases. The cyclically-constrained γ-amino acid residues incorporated into homogeneous γ-peptide backbones are useful probes in the study of chemical and enzymatic interactions involving natural proteins. Also, the compounds disclosed herein add greatly to the γ-peptide field, in terms of both the number of alternative secondary structures that can be accessed and the intrinsic stability of those secondary structures. The subject compounds are useful probes because the cyclically-constrained residues create secondary structures with high conformational stability at short oligomer lengths that are also resistant to enzymatic degradation. The invention thus enhances the control over γ-peptide folding preferences, thereby providing a larger "toolbox" of probes to be used in investigating the function of naturally-occurring proteins.
>
> Thus, the subject compounds are useful to implement a method of probing, disrupting, or mimicking binding interactions between two protein molecules or fragments thereof. The method comprises introducing to an in *vivo*, *in vitro*, or *ex vivo* reaction between two proteins, an unnatural polypeptide compound as described herein. Any effect of the added compound on thermodynamic or kinetic parameters of the binding interaction

> between the two protein molecules or fragments thereof is then measured. Because the subject compounds are conformationally similar to conventional α-polypeptides, but not subject to enzymatic degradation, the results provide valuable information regarding the interactions between large protein molecules.

The utility recited in the '384 Patent is exactly the same as the utility recited in the present application. For example, compare the above-quoted passage from the '384 Patent with Claim 11 of the present application as filed, and with the paragraph at page 15, lines 9-15 of the present application:

> A fifth embodiment of the invention is directed to a method of probing, disrupting, or mimicking binding interactions between two protein molecules or fragments thereof, the method comprising: in an *in vivo*, *in vitro*, or *ex vivo* reaction between the two proteins, introducing to the reaction an unnatural polypeptide compound as described hereinabove. Then, quantifying any effect of the added compound on the thermodynamic or kinetic parameters of the binding interaction between the two protein molecules or fragments thereof.

Note also that the compounds described in the '384 Patent include trimers, tetramers, and larger oligomers comprised entirely of γ-amino acid residues, at least one of which residues is cyclically constrained. Thus, the compounds described in the '384 Patent are more structurally similar to the compounds recited in the present claims than are the dipeptides described in the Seebach et al. paper. (Applicants take care to note that the '384 Patent is limited to a description of unnatural polypeptides consisting entirely of γ-amino acid residues. These compounds are related to, but patentably distinct from, the mixed α-, β-, and γ-polypeptides recited in the present claims.)

Based on: (1) the structural similarity of the compounds disclosed in the Seebach et al. paper and the '384 Patent to the compounds now claimed; (2) the specific utility described in the Seebach et al. paper and the '384 Patent; and (3) the contemporary appearance of the Seebach et al. paper and the '384 as compared to the earliest claimed priority date of the present application, Applicants respectfully submit that the Seebach et al paper and the '384 Patent satisfy both the first and second prongs of MPEP §2107(II): a person of ordinary skill in the art would immediately appreciate *why* the presently claimed

compounds are useful based on the characteristics of the invention, and the utility is specific, substantial, and credible. The claimed compounds have the same specific utility as described by Seebach et al. and in the '384 Patent. The shared characteristics between the Seebach et al. compounds, the '384 Patent compounds, and the claimed compounds are that they are unnatural polypeptides that have additional carbon atoms within the peptide backbone, and that, in the case of the '384 Patent, at least one of the residues must be cyclically constrained.

This is a structure-specific utility. It is not a utility shared by, for example, all proteins. The compounds described by Seebach et al., the '384 Patent, and the presently claimed compounds share a structural feature that gives them a specific utility, namely the ability to disrupt protein-protein interactions.

In further support of this contention, Applicants submit herewith a Rule 132 Declaration of inventor Sam Gellman. At paragraph 1 of his declaration, Dr. Gellman presents his credentials and his familiarity with the present application. At paragraph 2 of his declaration, Dr. Gellman notes that the work described in the declaration was performed in the United States, either by him personally or under his direction and supervision. At paragraph 3, Dr. Gellman states that the purpose of his declaration is two-fold: (1) to show that utility described in the application is well-understood by a chemist of ordinary skill; and (2) that the utility is credible and specific to the claimed compounds.

At paragraph 5 of his declaration, Dr. Gellman notes that the utility of the claimed compounds arises from their structure: "The claimed compounds adopt stable secondary conformation[s]." Moreover, the claimed compounds contain unnatural β- and/or γ-amino acid residues, thus making them less prone to being degraded by many protein-degrading enzymes. These qualities are specific to the structure of the claimed compounds.

At paragraph 5 of his declaration, Dr. Gelman definitively states that the utility presented in the application is well-established and well-understood to a chemist of ordinary skill. In particular, Dr. Gellman states that all of the claimed compounds "share the feature of having two or more unnatural amino acid residues, either β-amino acid residues or γ-amino acid residues." Because the compounds adopt stable secondary

conformations, as noted earlier, "they mimic the pharmacological properties of natural peptides," but are less susceptible to enzymatic degradation in the same fashion as natural peptides.

Specifically addressing the Seebach et al. paper, please see paragraph 6 of Dr. Gellman's declaration. Dr. Gellman notes the contemporaneous publication of the Seebach paper to the filing of the subject application. Dr. Gellman goes on to state that while Seebach's compounds are dipeptides (as contrasted to the tetrapeptides which are the smallest compounds claimed), Seebach's compounds are "closely related" to the present compounds because Seebach's compounds are constructed of γ-amino acid residues. Dr. Gellman goes on to state that the Seebach et al. paper is relevant to the utility of the present compounds because Seebach et al. made the compounds specifically to mimic the binding interactions between two peptides. Dr. Gellman goes on to conclude paragraph 6 of his declaration by noting that the Seebach et al. paper "clearly shows" that compounds falling with the same class as those now claimed have a utility that is well-known to peptide chemists (utility as peptido-mimetics) and that that utility is structure-based. The use of β-amino acid residues and γ-amino acid residues imbues the compounds with structure-specific utility.

Similarly, in paragraph 7 of his declaration, Dr. Gellman indicates that the '384 Patent discloses the same utility as disclosed in the present application. Dr. Gellman goes on to state that the compounds described in U.S. Patent No. 6,958,384 are oligomers comprised entirely of γ-amino acids, at least one of which is cyclically-constrained. Dr. Gellman than states that the compounds described in the issued patent are structurally similar to the presently claimed mixed α-, β, γ-oligomers. Thus, the presently claimed compounds have a well-established utility that was readily understood by one of skill in the art at the time the present application was filed.

At paragraph 8 of his declaration, Dr. Gellman further notes that chemical compound libraries. Dr. Gellman goes on to note that a chemist understands that such compound libraries are useful. See Exhibits B, C, and D, attached to Dr. Gellman's declaration for evidence of the commercial availability of such chemical libraries. In light

of the exhibits, Dr. Gellman concludes that there is a well-established utility for chemical libraries.

With respect to the second prong of MPEP §2107(II), that the utility is specific, substantial, and credible, Applicants note that the '384 Patent discloses the same specific, substantial, and credible utility as recited in the present application. Because the utility described in the '384 Patent is clearly well-established (the patent is available to the public), and because the '384 Patent is presumed to be in compliance with the utility requirement of §101, Applicants submit that the presently claimed compounds likewise have a specific, substantial, and credible utility.

The Office asserts, at page 5, first full paragraph of the Office Action, that disrupting protein-protein interactions is a generic utility. The Office goes on to ask "which specific protein-protein interactions are contemplated and disclosed to be disrupted by Applicant?" And "To what end are the interactions disrupted?" Applicants refer to Dr. Gellman's declaration to provide specific answers to the Examiner's questions.

Before addressing the remainder of Dr. Gellman's declaration, Applicants traverse the assertion that disrupting protein-protein interactions is a "generic" utility. The Office has not provided any basis upon which it concludes that interrupting protein-protein interactions is a "generic" utility. Applicants also traverse the requirement implicit in the first question that Applicants must "disclose" a utility. Where a utility is well-known in the art, there is no requirement that the Applicant actually "disclose" a utility within the application itself. Rather, when a §101 rejection is made by the Office, the burden is shifted to the Applicant to establish that a specific and substantial utility was well-established at the time of filing. See MPEP 2107(II)(B)(3)(ii):

> [In response to a utility rejection, the Applicant should] Provide evidence that one of ordinary skill in the art would have recognized that the identified specific and substantial utility was well-established at the time of filing. The examiner should review any subsequently submitted evidence of utility using the criteria outlined above. The examiner should also ensure that there is an adequate nexus between the evidence and the properties of the now claimed subject matter as disclosed in the application as filed. That is, the applicant

has the burden to establish a probative relation between the submitted evidence and the originally disclosed properties of the claimed invention.

Applicants respectfully submit that the documents referenced hereinabove and in Dr. Gellman's declaration show both a well-established utility and a probative relationship between the compounds described in the documents and the compounds claimed herein.

In answer to the Examiner's questions regarding utility, Applicants again refer to the Rule 132 declaration of Dr. Gellman.

At paragraph 9 of his Declaration, Dr. Gellman states the purpose of the experiments described in the declaration; namely to show that the claimed compounds have a specific, credible, and concrete utility. Dr. Gellman goes on to state that the utility asserted in the patent application is specific to the presently claimed compounds and that undue experimentation is not required to identify or to confirm this utility. Thus, the utility of the compounds as articulated is specific, credible, tangible and easily confirmed by a chemist of ordinary skill.

Starting at paragraph 10, Dr. Gellman provides some introductory comments regarding compounds that bind to specific protein surfaces. Dr. Gellman notes that traditional "small molecule" have been successful for enzyme inhibition, but less successful for generating protein-protein interaction antagonists. Dr. Gellman goes on to state that he and others have used unnatural oligomers with discrete folding propensities ("foldamers") to provide a rational basis to make molecules that block protein-protein interactions.

Starting at paragraph 11 and extending through paragraph 19 of his declaration, Dr. Gellman describes a series of experiments showing that compounds according to the present invention can block Bcl-$x_L$/BH3 domain interactions. As noted at the end of paragraph 10 of his declaration, the results of the experiments show that foldamer-based designs can provide tight-binding ligands for a large protein-recognition site ($K_i$ for compound 4 = 0.7 nM). The tight binding of chimeric ($\alpha/\beta+\alpha$)-peptides (peptides within the scope of the present claims) to Bcl-$x_L$ suggests that combining different foldamer scaffolds is also an effective (and perhaps general) strategy for protein ligand design.

As paragraph 12 of his declaration, Dr. Gellman states that interactions within the Bcl-2 protein family control the fate of a cell in response to cytotoxic stimuli. In short, this system is a substantial and credible system to disrupt because in many cancers, anti-apoptotic Bcl-2 proteins such as Bcl-$x_L$ are overexpressed and protect malignant cells from death (apoptosis) by direct interaction with pro-apoptotic proteins such as Bak and Bad. Thus, as Dr. Gellman states, interrupting the Bcl-$x_L$/Bak interaction is therapeutically useful.

Dr. Gellman goes on to state that many small molecule ligands for the BH3-recognition domain have been described, but that most have only modest activity ($IC_{50}$ values in competition binding assays typically $> 1\ \mu M$). Dr. Gellman opines that this outcome is perhaps due to the large surfaces buried in the Bcl-$x_L$/Bak 16-mer complex. A 16-residue peptide from the BH3 domain of Bak binds to a hydrophobic groove on Bcl-$x_L$ as an a-helix, burying four hydrophobic side chains (Val-74, Leu-78, Ile-81 and Ile-84), thus making this protein-protein interaction difficult to disrupt. Dr. Gellman indicates, however, that the experiments presented in the declaration show that compounds as claimed in the present application mimic the α-helical display of Bak side chains and are a good source of Bcl-$x_L$/Bak interaction antagonists. Dr. Gellman also notes that foldamers such as those currently claimed can be proteolytically stable, a distinct advantage relative to α-peptide inhibitors. The experiments described by Dr. Gellman use compounds containing both α- and β-amino acid residues. The compounds compete effectively with the Bak 16-mer for binding to Bcl-$x_L$, thus showing, by way of objective scientific evidence, that the utility described in the present application is substantial and credible.

Dr. Gellman's work focused on the 14/15-helix formed by α/β-peptides (oligomers with a 1:1 alternation of α- and β-amino acid residues along the backbone). See paragraph 13 of the declaration. Dr. Gellman and his co-workers designed Bcl-$x_L$ ligand candidates based on these secondary structures. These compounds fall within the scope of the present claims. The designs based on the 14/15-helix displayed significant activity in fluorescence polarization (FP) assays. The compound did interrupt the binding,although these α/β-peptides were not as effective as α-peptides corresponding to natural BH3 domain

sequences. For example, α/β-peptide 15-mer compound **1** (see page 7 of the declaration for the structure) displayed $IC_{50}$ = 40 μM ($K_i$ = 1.5 μM), while $IC_{50}$ = 0.67 μM ($K_i$ = 0.025 μM) for the unlabeled Bak 16-mer. See Figure 1 at page 8 of the declaration. Dr. Gellman explains that in compound **1** and related α/β-peptide designs, Leu-6 is intended to play the role of the Leu residue conserved in all BH3 domains reported to date (i.e., Leu-78 of Bak). Dr. Gellman speculates that the ACPC-3, $\beta^3$-homonorleucine-9 ($\beta^3$-hNle-9) and $\beta^3$-hPhe-13 residues of compound **1** also contribute to the hydrophobic surface required for binding to the BH3-recognition cleft of Bcl-$x_L$. Arg-4 and Asp-11 of compound **1** may be involved in electrostatic interactions with residues on the edge of the Bcl-$x_L$ cleft, as proposed for analogous residues in the Bak 16-mer. The significance of this experiment is that compounds according to the present invention bind to the BH3 domain (thereby disrupting the action of this physiologically important system).

At paragraph 14 of his declaration, Dr. Gellman and his co-workers examined chimeric oligomers in which either the N-terminal portion or the C-terminal portion of compound **1** is replaced by an α-amino acid segment based on an α-peptide known to bind tightly to Bcl-$x_L$. Thus, the (α/β+α) oligomer **2** contains the first nine residues of α/β-peptide **1**, but the last six α-residues are related to the C-terminal segment of the Bak 16-mer, with Phe-13 of compound **2** intended to correspond to Ile-84 of Bak. In (α+α/β) oligomer **3**, the first nine residues correspond to positions 72-81 of Bak with Val-74 replaced by Leu; the final seven residues correspond to the C-terminal portion of α/β-peptide **1**. These complementary chimeric analogues of compound **1** show improved activities in the FP assay: for (α/β+α) oligomer **2**, $IC_{50}$ = 0.059 μM ($K_i$ = 0.0019 μM), while for (α+α/β) oligomer **3**, $IC_{50}$ > 700 μM. See Fig. 1 of the declaration. Thus, compoudn **2** is 10-fold **more potent** than the Bak 16-mer itself. The significance of this result, as noted by Dr. Gellman, is that it shows that the 14/15-helical α/β-peptide scaffold is well-suited to occupy at least a portion of the BH3-recognition cleft on Bcl-$x_L$. Again, this system plays an important role in the growth and proliferation of cancer cells.

At paragraph 15 of his declaration, Dr. Gellman indicates that several control studies were conducted with (α/β+α) oligomer **2** and related compounds. The hexa-α-

peptide corresponding to the C-terminal segment of compound **2** (Ac-GDAFNR-$NH_2$) at 500 $\mu$M displayed **no** interaction with Bcl-$x_L$ in the FP assay (see Figure 1 of the declaration). Thus, concludes Dr. Gellman, the $\alpha$-peptide segment of chimeric oligomer **2** is probably **not** the dominant contributor to Bcl-$x_L$ binding affinity.

At paragraph 16 of his declaration, Dr. Gellman studies the binding of compound **2** to $^{15}N$-labeled Bcl-$x_L$. This was accomplished using [$^1H$,$^{15}N$]-HSQC NMR measurements (see Figure 2 of the declaration). ("HSQC" designates "heteronuclear single quantum correlation." HSQC-NMR is a high-sensitivity, 2-dimensional NMR procedure wherein the signal-to-noise ratio is improved using an inverse pulse sequence that transfers from protons to the heteronucleus - in this case to $^{15}N$ nuclei.) Most of the Bcl-$x_L$ amide N-H cross peaks were significantly shifted upon addition of 50 $\mu$M of compound **2** to 100 $\mu$M Bcl-$x_L$. See Figure 2A, at page 9 of the declaration. The pattern of shifts and resonance broadening induced by addition of compound **2** (a mixed $\alpha/\beta$-polypeptide according to the present claims) are comparable to the effects induced by addition of the Bak 16-mer $\alpha$-peptide itself (see Figure 2B). Again, the significance of this result is that it shows that compound according to the present invention can interrupt protein-protein binding.

At paragraph 17 of his declaration, Dr. Gellman describes making a fluorescein-labeled derivative of compound **2**, designated "Flu-2." This derivative was prepared to compare binding to Bcl-$x_L$ with binding to unrelated proteins. Direct FP titration of 50 nM of Flu-2 with protein yielded a $K_d$ = 0.014 $\mu$M for Flu-2 binding to Bcl-$x_L$ (see Figure 3 of the declaration). In contrast, no binding to bovine $\gamma$-globulin (BGG) could be detected at 500 $\mu$M BGG, and the onset of binding to bovine serum albumin (BSA) occurred above 10 $\mu$M BSA (Figure 3). Thus, binding of Flu-2 to BGG or BSA is **at least $10^3$-fold weaker** than binding to Bcl-$x_L$. Notably, Dr. Gellman states that both BGG and BSA are promiscuous receptors for hydrophobic ligands. Dr. Gellman states that this result is **highly significant** because the failure of Flu-2 to bind tightly to either of these proteins indicates that the affinity of compound **2** for Bcl-$x_L$ is not simply the result of its hydrophobicity, but instead reflects complementarity to the BH3-recognition cleft.

As a further test of this complementarity, Dr. Gellman compared ($\alpha/\beta+\alpha$) oligomer **4** and its enantiomer in the competition FP assay (Figure 4). Oligomer **4** is an isomer of compound **2** in which $\beta^3$-hNle-9 has been replaced by $\beta^3$-hLeu. Dr. Gellman states that this small change leads to slightly improved affinity for Bcl-$x_L$ ($IC_{50}$ = 0.029 $\mu$M, $K_i$ = 0.0007 $\mu$M for 4). The enantiomer of compoumd **4**, however, displays much lower affinity for Bcl-$x_L$ ($IC_{50}$ > 1000 $\mu$M). Again, this result is significant because it indicates that the affinity shown is not simply the result of the hydrophobicity of compound **4**.

In paragraph 18 of his declaration, Dr. Gellman describes an experiment wherein the folding of ($\alpha/\beta+\alpha$) oligomer **5** in $CD_3OH$ was examined by 2D NMR.[14] Compound **5** has two modifications relative to compound **2** (Ala-2 → Lys and Lys-8 → Ile), which moderately diminish binding to the BH3-recognition cleft of Bcl-$x_L$ ($IC_{50}$ = 0.40 $\mu$M). Good dispersion of $^1H$ resonances was observed for compound **5**, which allowed assignment of many NOEs between backbone protons. Numerous i,i+3 NOEs were observed along the entire length of compound **5** (see Figure 5 of the declaration, at page 12). Of particular importance are the three $\alpha$-residue $H_\alpha$(i) → $\beta$-residue $H_\alpha$(i+3) NOEs in the $\alpha/\beta$-peptide segment of compound **5**. This NOE pattern is predicted for the 14/15-helix but not for the 11-helix. In contrast, $\alpha$-residue $H_\alpha$(i) → $\alpha$-residue NH(i+2) NOEs are predicted for the 11-helix but not for the 14/15-helix, and **none** of these NOEs is observed for compound **5**. Thus, the NMR data suggest that compound **5** has a substantial propensity to adopt the 14/15-helical secondary structure in its N-terminal region, a propensity that is likely to be manifested also by closely related molecules such as compound **2**. Dr. Gellman also notes that the i,i+3 NOEs involving the C-terminal $\alpha$-peptide region of compound **5** suggest that the 14/15-helical $\alpha/\beta$-segment can nucleate helix formation in the short $\alpha$-peptide segment.

At paragraph 19 of his declaration, Dr. Gellman draws a number of conclusions from the experiments. Notably, Dr. Gellman concludes that the results of the experiments are significant because they reflect the exact utility that is stated in the application. The subject compounds mimic natural protein conformations in solution, but are resistant or immune to proteolytic degradation by proteases and peptidases. The compounds are thus useful probes in the study of chemical and enzymatic interactions involving natural

proteins. As shown above, compounds according to the present invention provide tight-binding ligands for a large protein-recognition site ($K_i$ for compound **4** = 0.7 nM). Dr. Gellman also concludes that the tight binding of chimeric ($\alpha/\beta+\alpha$)-peptides to Bcl-$x_L$ indicates that combining different foldamer scaffolds is also an effective strategy for protein ligand design.

At paragraph 20 of his declaration, Dr. Gellman also includes data showing that compounds according to the present invention inhibit viral infection. Here, $\alpha/\beta$-peptides falling within the scope of the present claims are shown to inhibit the infection of human fibroblast cells with human cytomegalovirus (CMV), which is a source of human disease. Dr. Gellman includes data for several compounds in a graph (Figure 6 of the declaration). (The structures of the compounds tested are shown in Figure 7.) As Dr. Gellman states at paragraph 20, in this assay, the virus expresses green fluorescent protein (GFP). The green fluorescence is thus tracked to learn how many cells have been infected with the virus. For compounds VI-139 and VI-145, the data show significant inhibition of viral infection when the $\alpha/\beta$-peptide is present at 50 $\mu$M. This results are significant because, as Dr. Gellman state, the results show that $\alpha/\beta$-peptides according to the present claims can block CMV infection of target cells, which is a biomedically valuable, structure-specific property.

In light of Dr. Gellman's declaration, it is respectfully submitted that the Applicants have produced a cogent body of evidence showing that the presently claimed compounds have a specific, substantial, and credible utility.

Lastly, at page 5, second full paragraph of the Office Action, the Office states that while chemical libraries are commercially available, they are sold as "research tools," which are "clearly delineated" by MPEP §2107.01(I) as being a utility which is not substantial. Applicants respectfully submit that there is no such "clear delineation" within the MPEP regarding "research tools." MPEP §2107.01(I)(C) is titled "Research Tools," but this section of the MPEP explicitly states that "Labels such as 'research tool'... **are not helpful** in determining if an applicant has identified a specific and substantial utility for the invention." (Emphasis added.) While perhaps the phrase "research tool" was used only as a shorthand expression, it appears that the Office has labeled the claimed invention a "research tool," and

has rejected the claims, at least in part, on that basis. Based on the explicit language of MPEP §2107.01(I)(C), Applicants submit that this is an improper basis upon which to support a rejection under §101.

MPEP §2107.01 indicates that "practical utility" is a shorthand way of attributing "real-world" value to claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner which provides some immediate benefit to the public. This section of the MPEP goes on to state that practical considerations require the Office to rely on the inventor's understanding of his or her invention in determining whether and in what regard an invention is believed to be "useful." The Examiners are thus explicitly encouraged by the MPEP to "focus on and be receptive to assertions made by the applicant that an invention is 'useful' for a particular reason." Applicants note that the *specific* utility recited in the specification is *specific* to the subject matter claimed because of their cyclically constrained structure. This structure is not shared by all peptides, nor even by non-cyclically constrained β-peptides or non-constrained γ-peptides. In short, the claimed compounds have a specific quality not shared by natural polypeptides, and not shared by all peptido-mimetics as a general class. All of the subject compounds contain at least two cyclically constrained residues that give them a limited range of conformations not exhibited by other types of peptides, and thus making them ideally suited to disrupt protein-protein interactions, as evidenced in Dr. Gellman's declaration.

In terms of substantiality, Dr. Gellman's declaration clearly shows that compounds falling within the scope of the present claims can disrupt protein-protein interactions in Bcl-2 proteins, an anti-apoptotic protein that plays a critical role in the proliferation of many cancers. Compounds falling within the scope of the present claims can also inhibit the infection of fibroblast cells by cytomegalovirus. These are substantial, real-world, specific utilities. As noted by the MPEP §2101.01 itself, <u>any</u> reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility. Applicants respectfully submit that the evidence submitted herewith corroborates the specific, substantial, and credible utility set forth in the application as filed.

Applicants therefore respectfully submit that the application as filed, coupled with the evidence filed herewith, establishes a specific, substantial and credible utility for compounds now claimed. Applicants therefore request that the rejection of the claims under §101 and §112, first paragraph (enablement) be withdrawn.

**Objection to Claims 4 and 6:**

This objection has been addressed by appropriate amendment to Claims 4 and 6 in accordance with the Examiner's recommendation. Specifically, and in keeping with conventional nomenclature for polypeptides, the left-hand "A" substituent has been defined to be hydrogen or an amino-terminus protecting group, while the right-hand "A" substituent has been designated "A' " and is now defined as a hydroxy group or a carboxy-terminus protecting group. Withdrawal of the objection is respectfully requested.

**Rejection of Claims 4 and 6 Under 35 USC §112, Second Paragraph:**

This rejection is believed to have been overcome, in part, by appropriate amendment to the claims, and is, in part, respectfully traversed.

This rejection is believed to have been overcome, in part, by removing the errant phrase "when V and W are not combined" from Claims 4 and 6. Applicants also note that their explicit intent is for the claims to cover compounds, that is the explicitly recited compounds **or** salts of the recited compounds. The claim language has been amended to reflect this intent.

Applicants respectfully traverse the Office's interpretation (at page 7 of the Office Action) that "The claim does not allow for X and/or Z to 'comprise' any more than a single amino acid, as the introductory recitation is that each X and each Z is..., " Applicants respectfully note that the Office's interpretation is contrary to the explicit definition provided in the specification itself.

Please see the paragraph at page 15, lines 16-21 of the specification as filed (emphasis added):

> As used in the specification and the claims, the word "independently," when referring to the nature of a variable substituent, explicitly means that **each** appearance of the defined

> substituent within a molecule can be different. Thus, for example, in a molecule according to the present invention such as A—$X_3$—$Z_3$—B (where Y is a single bond, A is hydrogen, and B is hydroxy), **each** appearance of X and **each** appearance of Z can vary independently within the molecule. Thus, according to this **explicit** definition, the molecule A—$X_3$—$Z_3$—B explicitly encompasses the molecule A—X'—X''—X'''—Z'—Z''—Z'''—B , where X' may the same as or different from X'', and X'' may be the same as or different from X'''. Likewise, Z' may the same as or different from Z'', and Z'' may be the same as or different from Z'''.

Thus, "each" appearance of X or Z as recited in the claims, and as described in corresponding language from the specification (see the above-quoted passage) may be the some or different. Applicants respectfully submit that there is nothing unclear, indefinite, or unambiguous in this explicit definition. The variables X and Z as presented in the claims are accompanied by subscripts ("a" and "c") which are positive integers. Thus the claim clearly indicates that there can be more than one X substituent and more than one Z substituent. In short, when the integers "a" and "c" are greater than 1, "each" appearance of the multiple X or Z substituents may be different, as noted in the specification at page 15. Thus, it is appropriate to include the grammatical construction "each X and each Y is..."

In the Office's comments, the language "each X and each X is" is highlighted and is quoted to support the Office's assertion that the claims do not allow for X or Z to be more than a single amino acid. Applicants respectfully note that this interpretation is inconsistent with the grammar used in Claims 4 and 6. When singling out an individual member of a group using the indefinite pronoun "each," the proper verb is "is." But that grammar in no way implies or requires that there be only one of the items being described. For example, if one were looking at a plurality of cars in a dealer's parking lot, and describing various characteristics of those cars, one would say "Each car is a Honda Civic. Each car is a different color. Each car is red, white, or blue." The present claims use the same type of grammar. And, as noted above, the specification provides an explicit definition to this effect.

In light of the amendments to the claims, and the above remarks, Applicants submit that the rejection of Claims 4 and 6 under §112, second paragraph, has been overcome. Withdrawal of the rejection is respectfully requested.

**Rejection of Claims 4-6 Under §102(b) In View of Huck et al. (2000) Organic Letters 2(17):2607-2610:**

As applied to Claim 5, this rejection has been rendered moot by cancellation of the claims.

As applied to Claims 4 and 6, this rejection is believed to have been overcome by appropriate amendment to claims. Specifically, both of Claims 4 and 6 have been amended in two respects, thereby overcoming this rejection. First, the definition of $R^{15}$ and $R^{16}$ has been amended to recite that these two substituents are not simultaneously hydrogen. Second, the "Y" substituent is now solely a single bond.

As amended, Applicants respectfully submit that the claims are neither anticipated by, nor rendered obvious in view of, the Huck et al. paper.

Withdrawal of this rejection is respectfully requested.

## CONCLUSION

In light of the above amendment and remarks, Applicants submit that the application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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**I certify that this paper is being deposited with the U.S. Postal Service as First-Class Mail, postage-paid, in an envelope addressed to Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450**

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